PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference P10553PC	**FOR FURTHER ACTION**	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/EP 03/06207	International filing date *(day/month/year)* 11.06.2003	Priority date *(day/month/year)* 11.06.2002
International Patent Classification (IPC) or both national classification and IPC A61K38/00		
Applicant CELLARTIS AB et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 8 sheets, including this cover sheet.

   ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the opinion
   - II ☐ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☒ Lack of unity of invention
   - V ☒ Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
09.01.2004	13.09.2004
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized Officer Merckling-Ruiz, V Telephone No. +49 89 2399-8590

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/EP 03/06207

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:

Description, Pages

1-37 as originally filed

Claims, Numbers

1-45 as originally filed

Drawings, Sheets

1-5 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

   These elements were available or furnished to this Authority in the following language: , which is:

   ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).

   ☐ the language of publication of the international application (under Rule 48.3(b)).

   ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

   ☐ contained in the international application in written form.

   ☐ filed together with the international application in computer readable form.

   ☐ furnished subsequently to this Authority in written form.

   ☐ furnished subsequently to this Authority in computer readable form.

   ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

   ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

   ☐ the description, pages:

   ☐ the claims, Nos.:

   ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)).

   (Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

   ☐ the entire international application,

   ☒ claims Nos. 17, 18, 34, 37, 40 (part), 41-45

   because:

   ☒ the said international application, or the said claims Nos. 17, 18, 34, 37 relate to the following subject matter which does not require an international preliminary examination (specify):

   see separate sheet

   ☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

   ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

   ☒ no international search report has been established for the said claims Nos. 40 (part), 41-45

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

   ☐ the written form has not been furnished or does not comply with the Standard.

   ☐ the computer readable form has not been furnished or does not comply with the Standard.

IV. Lack of unity of invention

1. In response to the invitation to restrict or pay additional fees, the applicant has:

   ☐ restricted the claims.

   ☒ paid additional fees.

   ☐ paid additional fees under protest.

   ☐ neither restricted nor paid additional fees.

2. ☐ This Authority found that the requirement of unity of invention is not complied with and chose, according to Rule 68.1, not to invite the applicant to restrict or pay additional fees.

3. This Authority considers that the requirement of unity of invention in accordance with Rules 13.1, 13.2 and 13.3 is

☐ complied with.

☐ not complied with for the following reasons:

4. Consequently, the following parts of the international application were the subject of international preliminary examination in establishing this report:

☐ all parts.

☒ the parts relating to claims Nos. 1-39 and 40 (part) .

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	
	No:	Claims	1-4, 7-17, 19-21, 40 (NO)
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-4, 7-21, 40 (NO)
Industrial applicability (IA)	Yes:	Claims	
	No:	Claims	1-16, 19-32, 35-36, 38-40 (YES), 17-18, 34, 37 see separate sheet

2. Citations and explanations

see separate sheet

1. Reference is made to the following documents :

D1: DE 199 21 537 A (HOERSCH DIETER) 23 November 2000 (2000-11-23)

D2: DATABASE WPI Section Ch, Week 199320 Derwent Publications Ltd., London, GB; Class A96, AN 1993-164366 XP002258007 & JP 05 097694 A (DENKI KAGAKU KOGYO KK) 20 April 1993 (1993-04-20)

D3: LACROIX A: "Recepteurs illicites dans le syndrome de Cushing surrenalien" ANNALES D'ENDOCRINOLOGIE, vol. 62, no. 2, 2001, pages 185-188, XP002258002 ISSN: 0003-4266

D4: WO 00/58360 A (FLATT PETER RAYMOND ;HARTE FINBARR PAUL MARY O (GB); UNIV ULSTER () 5 October 2000 (2000-10-05)

D5: EP-A-0 479 210 (SANWA KAGAKU KENKYUSHO CO) 8 April 1992 (1992-04-08)

D6: WO 98/24464 A (UNIV BOSTON) 11 June 1998 (1998-06-11)

D7: TRÜMPER A ET AL: "Glucose-dependent insulinotropic polypeptide is a growth factor for beta (INS-1) cells by pleiotropic signaling." MOLECULAR ENDOCRINOLOGY (BALTIMORE, MD.) UNITED STATES SEP 2001, vol. 15, no. 9, September 2001 (2001-09), pages 1559-1570, XP002269317 ISSN: 0888-8809

D8: KAPLAN ANDREW M ET AL: "Gastric inhibitory polypeptide (GIP) binding sites in rat brain" PEPTIDES (TARRYTOWN), vol. 15, no. 2, 1994, pages 297-302, XP002258003 ISSN: 0196-9781

D9: COLE S L ET AL: "The identification of glucose insulinotropic polypeptide (GIP) in rat sensory ganglia and its regulation by somatostatin" REGULATORY PEPTIDES, vol. 102, no. 1, 15 October 2001 (2001-10-15), page 52, XP002258004 5th International Symposium on VIP, PACAP, Secretin, Glucagon and Related Peptides;Santa Barbara, CA, USA; November 04-08, 2001 ISSN: 0167-0115

D10: EL-SALHY M ET AL: "Immunohistochemical investigations of neuropeptides in the brain, corpora cardiaca, and corpora allata of an adult lepidopteran insect, Manduca sexta (L)." CELL AND TISSUE RESEARCH. GERMANY, WEST 1983, vol. 232, no. 2, 1983, pages 295-317, XP002258005 ISSN: 0302-766X

D11: R.J. BOLLAG ET AL: "Glucose-dependent insulinotropic peptide is an integrative hormone with osteotropic effects" MOLECULAR AND CELLULAR ENDOCRINOLOGY, vol. 177, 2001, pages 35-41, XP002258006 Elsevier Science Ireland Ltd. ISSN: 0303-7207

D12: EP-A-0 186 181 (SYNTEX INC) 2 July 1986 (1986-07-02)

D13: DIXON K N ET AL: "GASTRIC INHIBITORY POLYPEPTIDE IN ANOREXIA NERVOSA" INTERNATIONAL JOURNAL OF EATING DISORDERS, vol. 4, no. 4, 1985, pages 597-604, XP002269318 ISSN: 0276-3478

D14: WO 03/030946 A (NOVARTIS AG ;GOLIGHTLY DOUGLAS (US); HUGHES THOMAS (US); SAKHUJA K) 17 April 2003 (2003-04-17)

In addition, the following documents are cited, that were not cited in the Search Report (copies are appended thereto) :

D15 : Dauphinée et al. "Peptide suppression of breast cancer growth : in search of mechanisms by identification of cellular targets", Breast cancer research and treatment, vol. 64 No.1, page 109 (Nov. 2000)
D16 : Miyawaki et al. "Inhibition of GIP/GIPR axis prevents obesity", Diabetologia, vol. 44 Supplement 1, page A18 (August 2001).

Regarding point III

2. Claims 17, 18, 34 and 37 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(I) PCT).

Regarding point V

First invention (claims 1-21, and 40 in part)

3. Pharmaceutical compositions comprising GIP or analogues thereof are anticipated in D1, D2, D4 and D5. These documents also disclose the use of GIP in the treatment of wounds (D2) or diabetes (D1, D4, D5). Claims 1-4, 7-16 and 40 (in part) are not novel.

3.1 The prior art does not disclose the use of GIP for treating diseases/conditions caused

by loss of cells in the nervous system. Claims 5-6 are new.

3.2 The use of GIP antagonists for treating conditions characterized by cellular hyperproliferation is disclosed in D3 (Cushing's syndrome, adenoma), D12 (pancreatic islet cells hyperplasia) and D15 (breast cancer). Claims 17, 19 and 20-21 are not new.

3.3 There is no disclosure of an anti-GIP antibody in the prior art. Claim 18 is novel.

4. The problem solved in claims 5-6 is to provide an agent for treating conditions caused by loss of cells in the peripheral or central nervous system. The solution is the use of GIP. D9, regarded as the closest prior art, discloses the expression of GIP in rat ganglia. The present application shows that GIP increases the proliferation of rat hippocampal cells in vitro and in vivo (see examples 4-6). The application demonstrates a technical effect that was neither disclosed nor suggested in the prior art. The subject-matter of claims 5-6 seems to involve an inventive step.

4.1 The problem solved in claim 18 is to provide an agent for treating diseases/conditions caused by hyperproliferation of cells.
Prior art document D3 discloses the use of ocreotide (a compound that inhibits the release of GIP) for alleviating Cushing's syndrome. On the other hand, D15 describes the inhibitory activity of GIP itself (not an antagonist of GIP) on breast cancer cells. The prior art gives contradictory informations regarding the potential use of GIP, or compounds that antagonize GIP activity, in the treatment of diseases caused by cellular hyperproliferation. The present application does not demonstrate any effect of GIP or GIP antagonist on the hyperproliferation of cells. There is no example of the manufacture of an anti-GIP antibody either. The subject-matter of claim 18 is merely wishful thinking, the application disclosing even less than the prior art on the claimed subject-matter. Inventive step cannot be acknowledged.

Second invention (claims 22-39 and 40 in part)

5. The composition of claim 40 is not new for the reasons given in point 3 above.

5.1 The use of GIP or a GIP antagonist in the treatment of weight-related diseases is not anticipated in the available prior art. Claims 22-39 are novel.

6. D16, which is the closest prior art, teaches that the inhibition of the GIP/GIPR interaction prevents obesity, which is the contrary of what is claimed in the present application (see claim 22, directed to the use of GIP in the treatment of obesity). The effect of Gip in lowering weight gain in rats is showed in example 8 or the application. Since the technical effect seems to be demonstrated, claims 22-39 would be inventive over the prior at teaching.